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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,694	03/28/2001	William Daniel Hillis	0450-0001	9199

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,694	HILLIS, WILLIAM DANIEL	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- Th MAILING DATE f this communication appears n the cover she t with the corresp ndenc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE filed on 8/22/2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *3,4,16,17,26,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-15,18-25,27-31 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/2003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's RCE filed on August 22, 2003 and the amendment filed on June 20, 2003 have been entered. The claims pending in this application are claims 1-39 with claims 3, 4, 16, 17, 26, and 32-35 withdrawn from consideration as the result of the species elections. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on June 20, 2003. The claims 1, 2, 5-15, 18-25, 27-31, and 36-39 will be examined.

PATENT APPLICATION PUBLICATION

2. Applicant's request for correcting US Publication No. US 2003/0134277 A1 filed on September 22, 2003 has been received by the office action. US PTO Publication branch will contact applicant in this subject matter.

Claim Objections

3. Claim 6 is objected to because of the following informality: "used for" should be "is used for".

4. Claim 22 is objected to because of the following informality: "used for" should be "is used for" .

5. Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim since claim 38 is much broader than claim 39 since claim 38 has limited the electric potential at the individual array sites of the substrate surface. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 5-15, 18-25, 27-31, and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2, 5-15, 18-25, 27-31, and 36-39 are dependent on claim 1.

8. Claim 1 is rejected as vague and indefinite in view of the phrase "wherein each of the at least two oligonucleotide probes has one nucleotide capable of base pairing with a nucleotide of at least two sets of two or more nucleotides, said set having one nucleotide common to all sets and lacking one nucleotide present in the target sequence segment" because it is unclear what means "at least two sets of two or more nucleotides". Please clarify.

9. Claim 1 is rejected as vague and indefinite. According to the second part of the claim, the hybridization can only occur if no mismatch exists at the position of interest. In view of the first part of the claim, in "contacting" step, it appears that a position of interest in each oligonucleotide is not complementary to the target sequence and appears to indicate that there is a mismatch at the position of interest in each oligonucleotide. Therefore, the hybridization of the analyte and at least two oligonucleotide probes can not occur in the claim, which is opposite to the phrase "all, some or none of the at least two oligonucleotide probes hybridize to the target sequence segment" and the preamble "to obtain information on a target nucleic acid analyte". Please clarify.

10. Claim 5 is rejected as vague and indefinite. First, the phrase "one of a set of two or more nucleotides" is confusing since it is unclear how many nucleotides can mean a set of two ore more nucleotides. Second, since the first part of the phrase only describes " a set", there is insufficient antecedent basis for "a first or second set" in the phrase. Please clarify.

11. Claims 6, 10, 14, and 22 are rejected as vague and indefinite. According above rejections made on claim 1, since the hybridization of the analyte and at least two oligonucleotide probes can not occur in claim 1, the method of claim 1 can not used for sequencing the target nucleic acid analyte as recited in claim 6, the detection recited in claims 10 and 14, and allelic analysis recited in claim 22.

12. Claims 18 and 21 are rejected as vague and indefinite. According above rejections made on claim 1, since the hybridization of the analyte and at least two oligonucleotide probes can not occur in claim 1, the hybridized target nucleic acid recited in claim 18 does not exist and the

method of claim 19 can not be used for genetic analysis. Furthermore, since there is no verb in claim 21, claim 21 is not a complete sentence. Please clarify.

13. Claim 20 is rejected as vague and indefinite because it is unclear that "hybridized target nucleic acids" in claim 18 and "hybridized nucleic acids" in claim 20 are identical or not. If "hybridized target nucleic acids" in claim 18 and "hybridized nucleic acids" in claim 20 are identical, "hybridized nucleic acids" in claim 20 should be changed to "the hybridized target nucleic acids" in order to correspond to "hybridized target nucleic acids" in claim 18. Please clarify.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

15. Claims 1, 6, 18, 19, 23, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Senapathy (US Paten No. 6,521,428, filed on November 4, 1999).

Note that this rejection was made in view of the ambiguity of claim 1.

Senapathy teaches shot-gun sequencing and amplification without cloning. In the method of sequencing a nucleic acid template, the method steps comprised: (a) providing a plurality of first primers, each first primer comprising (1) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence and a handle at an end of each first primer wherein the handle was one or more universal bases; (b) annealing the plurality of first primers to different locations on a nucleic acid template (ie., genomic DNA or cDNA), wherein at least one primer from within the plurality of first primers annealed specifically to the template; (c) extending the specifically annealed primer from step b) with a mixture of dNTPs and ddNTPs to generate a series of nucleic acid fragments; and (d) determining the nucleotide sequence of a first region of the template from the series of nucleic acid fragments (see first paragraph in column 5 and claims 19-24 in columns 25 and 26).

Regarding claims 1, 23, and 24, since each first primer comprises a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long, a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence and a handle at an end of each first primer wherein the handle is one or more universal bases and the universal base is capable of base pairing with either a purine or pyrimidine, two first primers are two oligonucleotide probes having one nucleotide (ie., one universal base) capable of base pairing with two or more nucleotides as recited in claim 1. Since at least two first primers anneal to different locations on a nucleic acid

template, there is no mismatch to be existed at the position of interest as recited in claim 1. Since both first primers have one or more universal bases at their handles and there is no universal base in the nucleic acid template (ie., the target nucleic acid analyte), both first primers have one nucleotide in common and lack one nucleotide present in the target sequence segment at the position that the universal base has occupied as recited in claim 1. Therefore, claim 1 is anticipated by Senapathy. Since genomic DNA or cDNA are used as a nucleic acid template, claims 23 and 24 are anticipated by Senapathy.

Regarding claim 6, since the method taught by Senapathy is used for sequencing a nucleic acid template, claim 6 is anticipated by Senapathy.

Regarding claims 18 and 19, in the method for amplifying a nucleic acid template, the method steps comprises: (a) providing a plurality of first primers, each first primer comprising (I) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3' to the region of fixed nucleotide sequence; (b) providing a plurality of second primers, each second primer comprising (I) a region of different fixed nucleotide sequence having a defined length of from about 5 to 15 bases long and (ii) a region of randomized nucleotide sequence having a defined length of from about 2 to 11 bases long located 5' to or 3 ' to the region of fixed nucleotide sequence, wherein the regions of fixed nucleotide sequence in the second plurality of primers is shorter than the regions of fixed nucleotide sequence in the first plurality of primers; and (c) amplifying a first region of the nucleic acid template with the plurality of first primers and the plurality of second primers, wherein at

least one primer from within each of the plurality of first primers and the plurality of second primers anneal specifically to the template (see lines 5-15 in column and claim 25 in column 26). Since a polymerase chain reaction is performed in the presence of a polymerase using at least a pair of primers, claims 18 and 19 are anticipated by Senapathy.

Therefore, Senapathy teaches all limitations recited in claims 1, 6, 18, 19, 23, and 24.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Senapathy (1999) as applied to claims 1, 6, 18, 19, 23, and 24 above, and further in view of Santamaria *et al.*, (US Patent No.5, 578, 443, published on November 26, 1996).

The teachings of Senapathy have been summarized previously, *supra.*

Senapathy does not disclose to use his method for a genetic analysis such as allelic analysis as recited in claims 21 and 22.

Santamaria *et al.*, teach DNA sequence-based HLA typing method. Their PCR and sequencing methods are used for a genetic analysis such as allelic analysis (see lines 9-47 in column 2 and lines 14-21 in column 4).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used the method recited in claim 1 for a genetic analysis (ie., allelic analysis) in view of the patents of Senapathy and Santamaria *et al.*. One having ordinary skill in the art would have been motivated to do so because Santamaria *et al.*., have successfully used a sequencing method for a genetic analysis (ie., allelic analysis) and the simple replacement of one kind of sequencing method (i.e., the sequencing method taught by Santamaria *et al.,*) from another kind of sequencing method (i.e., the sequencing method taught by Senapathy) for a genetic analysis would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955

Response to Arguments

(1) In page 10, fifth paragraph bridging to page 11, last paragraph of applicant's remarks, applicant argued that: (1) "the present invention does not strive to produce longer probes; rather, its aim is to use a smaller number of hybridizing probes for both sequencing and amplification,

while obtaining the same amount of information from the hybridization (specification, page 5, lines 21-23)."; and (2) "the probes of the present invention do not include a region of fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or within the region of fixed nucleotide sequence." and "the hybridization of the present invention is dependent on the determinate use of degenerate base pairing.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, although the examiner agrees with applicant "the present invention does not strive to produce longer probes; rather, its aim is to use a smaller number of hybridizing probes for both sequencing and amplification", "the probes of the present invention do not include a region of fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, flanking, or within the region of fixed nucleotide sequence." and "the hybridization of the present invention is dependent on the determinate use of degenerate base pairing.", these limitations are not in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Second, Senapathy does teach to use of degenerate base pairing since the primers taught by Senapathy have randomized nucleotide sequences and one ore more universal bases.

Conclusion

18. No claim is allowed.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
November 12, 2003